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Sentinel Lymph Node Biopsy in oral squamous cell carcinoma: Analysis of error in a cohort of 100 consecutive cases.

Abstract

Objectives: UK national guidelines (2016) recommend Sentinel Lymph Node Biopsy (SLNB) be offered to patients with early oral cancer (T1-T2 N0) where the primary site can be reconstructed directly. This study highlights pitfalls that can be avoided in SLNB technique in order to further improve outcomes.

Materials and Methods: Retrospective analysis of 100 consecutive patients was performed. Adverse events within the SLNB protocol or poor patient outcomes triggered a root cause analysis of the records.

Results and Discussion: Lymphatic drainage of tracer failed in 2 cases due to procedural errors. Two +SLNB patients developed neck recurrence after completion neck dissection, one due to missed micro-metastasis, the other due to extra nodal spread leading to under staging and under treatment. Two false negative (FN) cases would not have occurred if all the harvested SLN had been histologically analysed according to the SLN protocol.

Conclusions: The disease specific (96%) and disease free (92%) survivals were above expectations for a cohort where 33% had stage 3 disease. If all harvested nodes had been analysed by SLN pathology protocol then 2 out of 3 FN cases would have been detected and two deaths potentially avoided. The FN rate would have fallen from 8.3% to 2.7%. The overarching message is that minor protocol deviations can result in a detrimental patient outcome.

Introduction

Recent evidence confirms a survival advantage of elective neck dissection (END) over a watch and wait policy¹ in patients with early oral squamous cell carcinoma (OSCC) and a clinically N0 neck. Meta-analysis²⁻⁴ demonstrates that sentinel lymph node biopsy (SLNB)

can reliably identify early metastasis and restrict neck dissection (ND) to 20-30%⁵⁻⁷ with a positive (+) SLNB. United Kingdom guidelines (2016) recommended SLNB is offered to patients (T1-T2 N0) with OSCC following the example of Denmark and Holland where it is standard⁸.

SLNB has a sensitivity and specificity of 79%-87% but a recognised false negative rate (FN) of up to 14%⁵. Reporting positive results is necessary to gain confidence in a technique but more informative data is gained in analysing failure. This study undertakes a root cause analysis of any adverse event in 100 consecutive SLNB cases. The intention is to identify pitfalls that can be avoided to improve outcomes.

Materials and Methods

Retrospective analysis was undertaken of 100 consecutive patients with OSCC (CT/MRI T1-T2 N0) treated between 2005-2013. The sentinel lymph node (SLN) technique followed standard protocol⁹. One-day (20-40 MBq) and two-day injection protocols (40-80 MBq) were used depending on resource availability. Static and dynamic imaging was performed in all patients with the addition of SPECT/CT in the final 26 cases (>2011).

Surgery was performed using a blue dye optical tracer. Ipsilateral SLN's retrieved at the time of surgery were either a) hot or blue or b) hot and blue, with firm nodes also being sampled and weaker contralateral nodes on SPECT/CT or hand-held gamma probe being disregarded. Evaluation consisted of an initial H&E section and, if negative, serial sections with H/E and, pan-keratin AE1/AE3 staining at 150 micron intervals⁵. If more than three nodes were harvested or there was a clear drop in gamma counts between nodes, the highest gamma count one was taken as the SLN and processed through the full protocol. The remainder were processed by single section through the hilum and H&E staining. If the SLNs were negative it was assumed metastasis had not occurred and a watch and wait policy adopted. If positive, a level 1-4 completion neck dissection (CND) was undertaken. These CND's were examined

by a single H&E hilum section, or from multiple 2mm cassette thickness slices if the node was thicker than 5mm (Figure 1). In preparation for this review all nodes harvested at SLNB were submitted for re-analysis.

Contemporaneous data was stored in a bespoke database (InfoFlex v.5, CIMS Ltd. UK) consisting of demographics, performance status, lymphoscintigraphy findings, SLN status, SLNB complications and tumour status. The type, site, date and subsequent treatment of any recurrences were noted.

Failure was defined as recurrence at any site, death from disease, a FN SLNB, or failure to find a SLN. A FN SLNB was defined as a negative (-) SLNB with subsequent development of isolated neck squamous carcinoma metastasis.

Statistical analysis

R (R-Project, R Core Team) was utilised to perform the statistical analysis. Independent t-test was used to determine any statistical relationships between the patients' demographics and their outcomes. The differences between the groups that developed complications and those that didn't were compared with Chi-squared, Fisher's exact tests and Welch's two sample t-test. Statistical probabilities that were less than 0.05 were considered significant.

Results

Details of 100 consecutive patients with OSCC (cT1 74%: cT2 26%) N0 M0 were retrieved. In two cases lymphoscintigraphy failed to demonstrate a SLN but was effective in 98 patients, 86 ipsilateral to the tumour, 10 bilateral, and 2 contralateral. On average, 2.5 SLN's were retrieved per patient (range 1-6) with 19 patients having more than three excised, but in these patients only the hottest was subjected to the full histological SLNB protocol.

A total of 36 patients proved to have occult neck metastasis (26% of pT1 and 50% of pT2), 33 were identified by SLNB and the remainder discovered as isolated recurrence during follow up (Table 1). The FN rate was therefore 8.33%. There were 12 deaths giving a crude survival of 88%. Eight of these were new primary tumours and were censored in the outcome analysis. Four patients died from recurrence of the original carcinoma (disease specific survival of 96%). Three of these deaths may have been preventable (Table 2: Cases 3,7,8).

Of the 33 +SLNB cases, 32 had CND and one received radiation alone. This was an error of medical assessment. After SLNB this patient was too frail for CND and had RT that failed to cure the disease (Table 2: Case 8). If it had been predicted the patient would not manage the two separate procedures, END would have been performed during the primary resection. Statistical analysis was performed on the pathological tumour factors with significant factors demonstrated in Table 3.

Isolated neck recurrence

Seven patients (excluding Case 8) developed isolated neck recurrence (Figure 1), four after +SLNB and ND and 3 after FN SLNB.

The +SLNB cases (N=32) subsequently had a CND and in 78% (N=25) no further lymph node metastases were detected. Four (4/32) subsequently developed isolated neck recurrence. In two patients (Table 2: Cases 9, 10), this occurred in the un-operated contralateral neck and were rescued. In the other two (Table 2: Cases 6, 7), recurrence was ipsilateral and both died of disease. For both there was reason for adjuvant therapy but it was not prescribed. In Case 6 there was evidence of extra nodal spread and in Case 7, additional positive nodes at CND which were not detected by routine CND H&E evaluation. The micro-metastasis became evident only on serial section according to SLNB protocol of nodes retrieved at CND at the same neck level as the +SLN. These cases would consequently have been staged as N2 or N3 disease and so eligible for post-operative radiotherapy (PORT).

Three patients (Table 2: Cases 3, 4, 5) with -SLNB had isolated neck recurrence (FN). In two, only one of the harvested SLN was examined and reported as negative. On re-evaluation, metastases were present in adjacent SLN's not subjected to the full SLNB pathology protocol. The third FN (Case 5) was due to the shine-through phenomenon discussed later.

Local recurrence

One patient developed primary site recurrence (Table 2: Case 2). The original lesion was anterior FOM and the recurrence in the posterior FOM. This patient continued smoking with multiple episodes of non-attendance, finally re-attending with advanced disease. Pathological review showed inadequate excision margin of the primary tumour (1mm) and confirmed the -SLNB status. Review found the Multidisciplinary Meeting did not recommend PORT or re-excision due to poor patient compliance.

Complications of Surgery

Of 98 patients that underwent SLNB there were two complications directly attributable to the procedure – one superficial wound infection and one neck haematoma requiring return to theatre (no drain placed). General complications not directly attributable to the SLNB procedure consisted of a chest infection (managed with antibiotics) and a separate transient ischaemic attack two months post-surgery. Complications observed in patients returning for ND after a +SLNB has prompted a separate review that will be submitted soon.

Cause of Error

Imaging

In two patients, drainage of tracer was inadequate. One with a floor-of-mouth (FOM) tumour (23 MBq on a one-day protocol), showed no drainage at 80 minutes post injection. The submental nodal fields were surgically explored but no SLN identified. This is possibly one of two examples of the shine-through effect with the radiation cloud at the injection site obscuring the adjacent SLN.

The second case related to a lesion of the anterior tongue. A two-day protocol was intended but a one day delivered (20 MBq tracer injected). At surgery, it was felt that there might be sufficient residual radiation to allow appropriate detection. At the initial lymphoscintigraphy two SLN's were identified but these could not be found at surgery. Both necks were managed by observation and are without recurrence at five years.

Shine-through is considered a risk of FOM radiotracer injection. In the present series, there were 12 patients with FOM carcinomas, one patient developed a new primary and died of disease, the remainder are disease free. One failed drainage and one FN have (Table 2: Case 5) been attributed to this cause.

Errors of image interpretation lead to three recurrences'. SLN's identified on gamma scan were intentionally not harvested due to the weak signal on SPECT/CT and hand-held gamma probe. This resulted in isolated neck recurrence, one ipsilateral and two contralateral (Table 2: Cases 4, 9, 10)

Pathology

In four cases, downgraded nodes clear of metastasis on routine H&E were found to contain micro-metastasis on subsequent serial sectioning (Table 2: Case 1, 3, 4, 7). Two of these patients succumbed to their disease. No failures were ascribed to errors in pathological technique or interpretation.

Discussion

SLNB is a diagnostic test that identifies early metastasis, separating patients into a good prognostic group without metastasis and poor biological group with metastasis. In the former there is the option to de-escalate treatment and in the latter to do the opposite. In this series of patients staged by SLNB the disease specific survival was 96% despite a third having Stage 3 disease. The authors acknowledge the lack of a comparable non-SLNB cohort in presenting survival data, this requires a large prospective randomised control trial. Nevertheless, the

SLNB process was successful and analysis has identified areas where technique improvements could further improve results. The overarching message is that even minor deviation from SLNB protocol can be detrimental to patient outcome.

Lymphoscintigraphy failed in two cases (2%). In one (FOM), failure to image a SLN was probably due to the shine-through effect. This is where radiation uptake in submental SLN is obscured by the larger radiation dose at the FOM. The second failure was due to a protocol breach. A one-day radiation protocol was used for a two-day surgical case, meaning radiation had dissipated (half-life ~6 hrs) by the time of surgery. Consequently the SLN identified on the gamma scan could not be identified at the time of surgery. In retrospect the tracer dose should have been topped-up prior to surgery. The optimal radiation regime seems to be in the range of 15-20 MBq for a one day and 40-50 MBq for a two day SLNB protocol¹⁰.

Lessons were learned in interpreting Gamma images. Usually in lateralised tumours there are one or two obvious hot areas in the ipsilateral neck with weaker signals in second order nodes. If there is drainage to the contralateral neck, the signal is invariably weaker. Prior to this analysis, we considered a weak signal as inconsequential but it appears these should not be ignored as they depict bone-fide drainage potentially containing metastases.

The pathological preparation of the harvested SLN's is expensive in time and technique. Early in our practice we believed that the hottest gamma count node would most likely contain metastasis. This assumption was incorrect. Paradoxically when excess nodes are harvested (>3) it is usually because an obvious SLN can't be identified. Selecting the correct SLN is an operator sensitive procedure, improving with experience. When unusually high numbers are harvested there should be careful discussion between nuclear medicine, pathology and surgeons to decide which, if not all, should be processed as a SLN.

Two FN cases would have been eliminated as +SLN's were harvested but not examined. This would have reduced the FN rate to 2.78%.

Another issue highlighted by this review is that when the +SLN is followed by a negative CND (78% of cases), there should be caution ascribing a pN1(sn) status. Isolated recurrence occurred in the ipsilateral neck after CND in two pN1(sn) patients. Standard single H&E section evaluation of nodes does not reliably identify all micro-metastases. When CND nodes taken from the same level as the +SLN were analysed by serial section, additional micro-metastases were identified that had not been detected previously. The stage of disease was not N1(sn) but the equivalent of N2(sn) or N3(sn), categories not currently recognised in TNM8 but probably qualifying for adjuvant therapy. Data from the SENT trial showed metastasis additional to the SLN are usually found in the same nodal basin as the +SLN¹¹. After CND, a more detailed examination of nodes in the same level as the +SLN could improve staging.

The impact of adverse histological features on outcome was typical of other series. The presence of increased depth of invasion, perineural and sarcolemmal spread predicted for recurrent disease (Table 3) and were present in 53% +SLNB patients but only 17% of the -SLNB. However, of the 20 patients with these factors none developed local recurrence. The one patient who did was -SLNB and had close resection margins.

A general perspective has held that SLNB may not be reliable when evaluating cancer in the anterior FOM due to ‘shine-through’¹². Recurrent disease due to delayed diagnosis of neck disease through a FN report is difficult to rescue. Only 50% of cases can be successfully salvaged with maximal therapy (surgery + chemoradiotherapy). To eliminate this risk a submental dissection has been advocated for FOM cancers¹³. The ability to identify “hot” nodes in the submental area may improve using Lymphoseek, a receptor mediated lymphatic tracer which clears the injection site and concentrates within nodes¹⁴. Additional marker use such as blue dye and fluorescence may also be advantageous¹⁵.

Conclusion

Disease specific (96%) and disease free survival (92%) were excellent for a cohort of patients where 33% had stage 3 disease. The data shows that SLNB identified 92% of patients with occult metastasis, but if all harvested nodes had undergone serial section then 97% would have been identified giving a surgical FN rate of just 3%. Potential improvements in detection could have been achieved by harvesting gamma imaging faint contralateral nodes and ensuring all SLNB harvested nodes are evaluated by serial section through the SLNB protocol. Neck recurrence following CND proved fatal. If on routine H/E evaluation no additional nodal disease is detected, detailed analysis of CND nodes from the SLN nodal basin should be considered.

Conflicts of Interest

None

Acknowledgements

None

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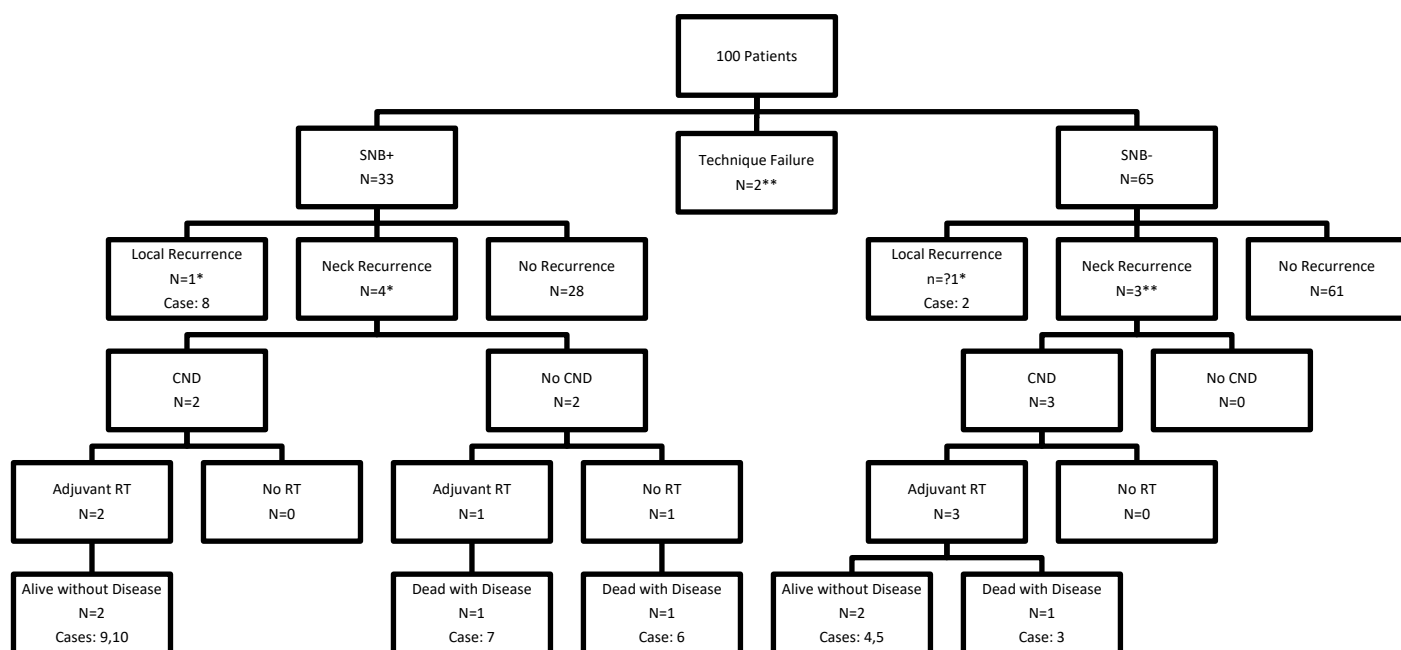
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* Denotes treatment failure not ascribed to sentinel lymph node procedure

** Denotes failure of SLN technique

Figure 1 - Patient Treatment Pathway and Outcome

Type of recurrence	SLNB Negative (n=65)	SLNB Positive (n=33)
Local	0	0
Local and Neck	0	0
Neck only	3	4
Local and Distant	0	0
Local, Neck and Distant	0	1
Total Recurrence	3	5

Table 1 – Disease Outcome by SLN Status

Case Number	Patient Factors	Scintigraphy	Surgery	Pathology	Site	Outcome	Recommendation
-SLNB							
1	Poor compliance with smoking cessation and follow up		Multiple primaries	Re-examination of additional nodes not treated as SLNB nodes identified micrometastasis	Local - New Primary	Alive no disease	Put all samples through SLNB protocol
2				4mm from nearest mucosal margin anteriorly. 1mm clearance at deep margin. Generalised field change.	Local – ? New Primary	Dead with disease	Patient selection
3				Only 1 of 4 nodes went through SLNB protocol, further histology showed viable tumour cells in a remaining SLN			
4				Re-review of imaging showed 2-3 less obvious ipsilateral nodes deeper in tissue - aberration of depth	Neck	Alive no disease	Put all samples through SLNB protocol Don't ignore faint nodes. Put all samples through SLNB protocol
5				Shine through - very hot injection site obscuring Level 1B (site of recurrence)	Neck	Alive no disease	Routine harvest of submental nodes.
+SLNB							
6	Recurrence at site of carotid bifurcation - inoperable		Missed node	Slides correctly reported. However SCC was extranodal within lymphatics and could account for extranodal recurrence	Neck	Dead with disease	Detailed examination of CND nodes around SLN when only one SLNB positive
7				Additional micrometastases were present in CND that could have upstaged the neck - micrometastasis deposit small and away from hilum	Neck	Dead with disease	Detailed examination of CND nodes around SLN when only one SLNB positive
8					Local, Neck, Distant	Dead with disease	Patient selection
9				Pre op FNA was negative of contralateral nodes, contralateral nodes ignored at SLNB	Neck	Alive no disease	Don't ignore faint nodes.
10				Hottest contralateral node taken, two faint delayed ipsilateral nodes due to depth ignored	Neck	Alive no disease	Don't ignore faint nodes

Table 2 – Identified Errors Case Summaries

		Negative	Positive	Welch Two sample t-test	
Depth of Invasion (mm)		3.59	7.52	<0.0005	
		Negative	Positive	Total Patients	Fisher's exact test
Perineural	Total	17 (61%)	11 (39%)	28	0.0078
	No	43 (74%)	15 (26%)	58	
	Yes	2 (22%)	7 (78%)	9	
Sarcolemmal	Total	18 (60%)	12 (40%)	30	0.0065
	No	40 (77%)	12 (23%)	52	
	Yes	4 (31%)	9 (69%)	13	

Table 3 - Significance of Primary Carcinoma Adverse Pathological Features by SLNB Result